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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/633,093	08/04/00	GREENBERGER J	07787-004003

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EXAMINER	
LI,Q	
ART UNIT	**PAPER NUMBER**
1632	4

DATE MAILED: 07/31/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Offic Action Summary	Application No. 09/633,093	Applicant(s) GREENBERGER ET AL.	
	Examiner Janice Li	Art Unit 1632	

-- The MAILING DATE of this c mmunication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The preliminary amendment filed on August 4, 2000 has been entered. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Currently, claims 1-11 are pending and under examination, claims 1 and 7-11 are amended, claims 12-20 are canceled.

Applicant's arguments with respect to claims 1-11 have been considered but are moot in view of new ground(s) of rejection triggered by the amendment to the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

These claims are vague, incomplete, and indefinite because the method steps are inconsistent with the preamble of the claim. The method is for obtaining a preparation of BMSCs, however, the first step is using a preparation of BMSCs, and the result of the method does not address obtaining of a preparation.

These claims are vague and indefinite because the claim recitation "comparable". The term "comparable to the level of expression" is not defined by the claim and encompasses low, medium and high levels of difference in comparison, the specification does not provide a standard for ascertaining the requisite degree of the comparable level, and one of the skill in the art would not be reasonably apprised of the scope of the invention.

These claims are vague and indefinite because the claim is incomplete. It is unclear how mere cryopreservation of the transfected BMSCs relates to the level of the exogenous gene expression. Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter that claims encompass as well as make clear the subject matter from which others would be precluded, *Ex parte Erlich*, 3 USPQ2d 1011 at 6.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, and 7-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Anderson et al* (US 5 399 346, 3-21-1995), taken with *Greenberger et al* (EP 0 381 490 A2, 8-8-90), and *Boswell et al* (Exp. Hematol 1983).

These claims are directed to a method comprising transfecting cultured bone marrow stromal cells with an exogenous gene, and cryopreserving the transfected BMSCs, wherein the level of expression of the exogenous gene is comparable to that of the transfected BMSCs that are not subsequently cryopreserved, wherein the BMSCs are obtained from bone marrow or bones of a vertebrate, particularly a mammal, a human, wherein the exogenous gene encodes a secreted peptide, a serum protein, a cytokine, a blood clotting factor, particularly a factor VIII or IX, or a cell surface molecule.

Anderson et al teach a method comprising transfecting cultured primary tumor infiltrating T-lymphocytes with a cytokine, such as TNF-α and IL-2, infusing the cells to a patient, and cryopreserving un-used portion of transfected cells for future infusion (column 14, lines 37-38). They then thawed these cells, expanded in culture, and infused the cell preparation to patients (column 17, lines 9-23). They go on to teach that the DNA which is used for transducing the human cells may be one whose expression product is secreted from the cells (secreted piptide), and may be any therapeutic proteins; examples of such product are a clotting factor, and T-cell receptor proteins (cell surface molecule). They further teach the cells used for transformation could be any human primary cells, particularly blood cells, mature or premature (columns 4-6). *Anderson et al* do not particularly teach bone marrow stromal cells.

However, before the effective filing date of the instant application, *Greenberger et al* teach that BMSCs may be more efficient in transgene expression than hematopoietic stem cells. (paragraph 4, page 2). *Boswell et al* teach cryopreservation of entire marrow cells, including hematopoietic and stromal cells. *Boswell et al* teach that BMSCs could transfer the microenvironment of the hematopoietic cells, therefore, is of functional significance for a successful bone marrow transplantation.

Therefore, it would have been obvious to one of ordinary skill in the art to modify the method taught by *Anderson et al* by simply substituting T lymphocytes or other blood primary cells with BMSCs as taught by *Greenberger et al* and *Boswell et al.* Although *Anderson et al* do not specify the levels of gene expression in their cryopreserved cells, they use the same method steps as instantly claimed, thus the levels of gene expression should be comparable to that of instantly claimed. The ordinary skilled artisan would have been motivated to modify the claimed invention using BMSCs alone or in combination with hematopoietic cells for an enhanced gene transfer and an enhanced regeneration of bone marrow. Furthermore, the purpose of cryopreservation of primary cells is to preserve the cell proliferation potential, and to avoid repeated clinical procedure in obtaining primary cells. The ordinary skilled artisan would have been sufficiently motivated to do so for any types of primary cells, at any stage of the experimentation,i.e. before or after DNA transfection, such as taught by *Anderson et al.* Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Anderson et al* (US 5 399 346, 3-21-1995), *Greenberger et al* (EP 0 381 490 A2, 8-8-90), and *Boswell et al* (Exp. Hematol 1983), as applied to claims 1-5, 7-10 above, and further in view of *Lozier et al* (Hum Gene Ther 1994).

These claims are directed to a method comprising transfecting cultured bone marrow stromal cells with an exogenous gene, and cryopreserving the transfected BMSCs, wherein the level of expression of the exogenous gene is comparable to that of the transfected BMSCs that are not subsequently cryopreserved, wherein the BMSCs are obtained from bone marrow or bones of a vertebrate, particularly a canine.

Anderson et al teach a method comprising transfecting cultured tumor infiltrating T-lymphocytes with a cytokine, such as TNF-α and IL-2, infusing the cells to a patient, and cryopreserving un-used portion of transfected cells for future infusion (column 14, lines 37-38). They then thawed these cells, expanded in culture, and infused the cell preparation to patients (column 17, lines 9-23). *Greenberger et al* and *Boswell et al* teach using BMSCs for gene therapy. *Anderson et al*, *Greenberger et al* and *Boswell et al* do not particularly teach a canine model.

However, before the effective filing date of the instant application, *Lozier et al* teach using a canine model for study of hemophilia B in human. They transfected canine BMSCs with canine factor IX, and teach the expression efficacy.

Therefore, it would have been obvious to one of ordinary skill in the art to employ canine BMSCs as taught by *Lozier et al* in the method described by *Anderson et al, Greenberger et al and Boswell et al* for studying human disease in a large mammal. The

ordinary skilled artisan would have been motivated to modify the claimed invention because a canine model is valid for studying human disease. Thus, the claimed invention as a whole was clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-5, 7-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Anderson et al* (US 5 399 346, 3-21-1995), *Greenberger et al* (EP 0 381 490 A2, 8-8-90), and *Boswell et al* (Exp. Hematol 1983), as applied to claims 1-5, 7-10 above, and further in view of *Lobb et al* (Biochem Biophy Res Com, 1991).

These claims are directed to a method comprising transfecting cultured bone marrow stromal cells with an exogenous gene, and cryopreserving the transfected BMSCs, wherein the level of expression of the exogenous gene is comparable to that of the transfected BMSCs that are not subsequently cryopreserved, wherein the BMSCs are obtained from bone marrow or bones of a vertebrate, particularly a canine, wherein the exogenous gene encodes an adhesion molecule, such as V-CAM.

Anderson et al teach a method comprising transfecting cultured tumor infiltrating T-lymphocytes with a cytokine, such as TNF-α and IL-2, infusing the cells to a patient, and cryopreserving un-used portion of transfected cells for future infusion (column 14, lines 37-38). They then thawed these cells, expanded in culture, and infused the cell preparation to patients (column 17, lines 9-23). *Greenberger et al* and *Boswell et al* teach using BMSCs for gene therapy and cryopreservation of BMSCs. *Anderson et al,*

Greenberger et al and *Boswell et al* do not particularly recite an adhesion molecule or VCAM.

However, before the effective filing date of the instant application, *Lobb et al* teach transducing human B and T lymphocytes expressing VCAM-1 (see abstract and methods). *Lobb et al* teach that VCAM1 as an surface molecule could selectively bind to CD4+ and CD8+ memory T cells and should prove useful for immune response *in vivo* (abstract and page 1503).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Anderson et al, Greenberger and Boswell et al*, by simply substituting a cytokine with VCAM as taught by *Lobb et al*. The ordinary skilled artisan would have been motivated to modify the claimed invention using the gene of interest with a reasonable expectation of success. Thus, the claimed invention as a whole was clearly *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen M Hauda can be reached on 703-305-6608. The fax numbers for the organization where this application or proceeding is assigned are 703-308-8724 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Kay Pinsky, whose telephone number is (703) 305-3553.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
July 20, 2001

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER